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(51) International Patent Classification ⁶: C07D 209/48, A61K 31/40, C07D 209/46	A1	(11) International Publication Number: WO 97/08143 (43) International Publication Date: 6 March 1997 (06.03.97)
(21) International Application Number: PCT/US96/14077 (22) International Filing Date: 29 August 1996 (29.08.96) (30) Priority Data: 08/520,710 29 August 1995 (29.08.95) US (71) Applicant (for all designated States except US): CELGENE CORPORATION [US/US]; 7 Powder Horn Drive, Warren, NJ 07059 (US). (71)(72) Applicants and Inventors: MULLER, George, W. [US/US]; 250 Windmill Court, Bridgewater, NJ 08807 (US). SHIRE, Mary [IE/US]; 8 Stone Street, North Plainfield, NJ 07060 (US). (74) Agent: NISSIM, Stuart, H.; Mathews, Woodbridge & Collins, P.A., Suite 306, 100 Thanet Circle, Princeton, NJ 08540 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: INHIBITORS OF TUMOR NECROSIS FACTOR ALPHA (57) Abstract Novel nitriles are inhibitors of tumor necrosis factor α and phosphodiesterase and can be used to combat cachexia, endotoxic shock, retrovirus replication, asthma, and inflammatory conditions. A typical embodiment is 3-Phthalimido-3-(3,4-dimethoxyphenyl)propionitrile.		

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INHIBITORS OF TUMOR NECROSIS FACTOR ALPHA

Background of the Invention

The present invention relates a method of reducing levels of TNF α in a mammal and to compounds and compositions useful therein.

5 TNF α , or tumor necrosis factor α , is a cytokine which is released primarily by mononuclear phagocytes in response to various immunostimulators. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase responses similar to those seen during acute infections and shock states.

10 Excessive or unregulated TNF α production has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome {Tracey *et al.*, *Nature* 330, 662-664 (1987) and Hinshaw *et al.*, *Circ. Shock* 30, 279-292 (1990)}; cachexia {Dezube *et al.*, *Lancet*, 335(8690), 662 (1990)}; and Adult Respiratory Distress Syndrome where TNF α concentration in excess of 12,000 pg/milliliters have been detected in pulmonary aspirates from ARDS patients {Millar *et al.*, *Lancet* 2(8665), 712-714 (1989)}. Systemic infusion of recombina-
15 nt TNF α also resulted in changes typically seen in ARDS {Ferrai-Baliviera *et al.*, *Arch. Surg.* 124(12), 1400-1405 (1989)}.

TNF α appears to be involved in bone resorption diseases, including arthritis where it has been determined that when activated, leukocytes will produce a bone-resorbing activity, and data suggest that TNF α contributes to this activity {Bertolini *et al.*, *Nature* 319, 516-518 (1986) and
20 Johnson *et al.*, *Endocrinology* 124(3), 1424-1427 (1989)}. It has been determined that TNF α stimulates bone resorption and inhibits bone formation *in vitro* and *in vivo* through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNF α may be involved in many bone resorption diseases, including arthritis, the most compelling link with disease is the association between production of TNF α by tumor or host tissues and
25 malignancy associated hypercalcemia {Calci. *Tissue Int. (US)* 46(Suppl.), S3-10 (1990)}. In Graft versus Host Reaction, increased serum TNF α levels have been associated with major complications following acute allogenic bone marrow transplants {Holler *et al.*, *Blood*, 75(4), 1011-1016 (1990)}.

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood
30 levels of TNF α and the most severe complication occurring in malaria patients. Levels of serum TNF α correlated directly with the severity of the disease and the prognosis in patients with acute malaria attacks {Grau *et al.*, *N. Engl. J. Med.* 320(24), 1586-1591 (1989)}.

TNF α also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibodies to TNF α completely blocked the silica-induced lung fibrosis in mice {Pignet *et al.*, *Nature*, 344:245-247 (1990)}. High levels of TNF α production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis {Bissonnette *et al.*, *Inflammation* 13(3), 329-339 (1989)}. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNF α as compared with macrophages from normal donors {Baughman *et al.*, *J. Lab. Clin. Med.* 115(1), 36-42 (1990)}.

TNF α is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow {Vedder *et al.*, *PNAS* 87, 2643-2646 (1990)}. TNF α also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin {Sherry *et al.*, *J. Cell Biol.* 107, 1269-1277 (1988)}. TNF α has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF α -induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells {Munro *et al.*, *Am. J. Path.* 135(1), 121-132 (1989)}.

Moreover, it is now known that TNF α is a potent activator of retrovirus replication including activation of HIV-1. {Duh *et al.*, *Proc. Nat. Acad. Sci.* 86, 5974-5978 (1989); Poll *et al.*, *Proc. Nat. Acad. Sci.* 87, 782-785 (1990); Monto *et al.*, *Blood* 79, 2670 (1990); Clouse *et al.*, *J. Immunol.* 142, 431-438 (1989); Poll *et al.*, *AIDS Res. Hum. Retrovirus*, 191-197 (1992)}. AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, *i.e.*, HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1 and HIV-2, infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected

with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNF α , are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably TNF α , in a HIV-infected individual aids in limiting the maintenance of T lymphocyte activation caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells {Rosenberg *et al.*, *The Immunopathogenesis of HIV Infection*, Advances in Immunology, 57 (1989)}. Cytokines, such as TNF α , have been shown to activate HIV replication in monocytes and/or macrophages {Poli *et al.* *Proc. Natl. Acad. Sci.*, 87, 782-784 (1990)}, therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression as stated above for T cells. Additional studies have identified TNF α as a common factor in the activation of HIV *in vitro* and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, *et al.*, *PNAS* 86, 2336-2340). This evidence suggests that a reduction of TNF α synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNF α {Folks *et al.*, *PNAS* 86, 2365-2368 (1989)}. A molecular mechanism for the virus inducing activity is suggested by TNF α 's ability to activate a gene regulatory protein (NF κ B) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) {Osborn *et al.*, *PNAS* 86, 2336-2340 (1989)}. TNF α in AIDS associated cachexia is suggested by elevated serum TNF α and high levels of spontaneous TNF α production in peripheral blood monocytes from patients {Wright *et al.* *J. Immunol.* 141(1), 99-104 (1988)}.

TNF α has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

Preventing or inhibiting the production or action of TNF α (e.g. with treatment with the compounds of this invention) is, therefore, predicted to be a potent therapeutic strategy for many inflammatory, infectious, immunological or malignant diseases. These include but are not

restricted to septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, radiation damage, and hyperoxic alveolar injury. Efforts directed to the suppression of the effects of TNF α have ranged from the utilization of steroids such as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies {Beutler *et al.*, *Science* 234, 470-474 (1985); WO 92/11383}.

The nuclear factor κ B (NF κ B) is a pleiotropic transcriptional activator (Lenardo, *et al.* Cell 1989, 58, 227-29). NF κ B has been implicated as a transcriptional activator in a variety of disease and inflammatory states and is thought to regulate cytokine levels including but not limited to TNF α and also to be an activator of HIV transcription (Dbaiho, *et al.* J. Biol. Chem. 1993, 17762-66; Duh *et al.* Proc. Natl. Acad. Sci. 1989, 86, 5974-78; Bachelier *et al.* Nature 1991, 350, 709-12; Boswas *et al.* J. Acquired Immune Deficiency Syndrome 1993, 6, 778-786; Suzuki *et al.* Biochem. And Biophys. Res. Comm. 1993, 193, 277-83; Suzuki *et al.* Biochem. And Biophys. Res Comm. 1992, 189, 1709-15; Suzuki *et al.* Biochem. Mol. Bio. Int. 1993, 31(4), 693-700; Shakhov *et al.* 1990, 171, 35-47; and Staal *et al.* Proc. Natl. Acad. Sci. USA 1990, 87, 9943-47). Thus, inhibition of NF κ B binding can regulate transcription of cytokine gene(s) and through this modulation and other mechanisms be useful in the inhibition of a multitude of disease states. The compounds claimed in this patent can inhibit the action of NF κ B in the nucleus and thus are useful in the treatment of a variety of diseases including but not limited to rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, septic shock, sepsis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS.

TNF α and NF κ B levels are influenced by a reciprocal feedback loop. As noted above, the compounds of the present invention affect the levels of both TNF α and NF κ B. It is not known at this time, however, how the compounds of the present invention regulate the levels of TNF α , NF κ B, or both.

Many cellular functions can be mediated by levels of adenosine 3',5'-cyclic monophosphate(cAMP). Such cellular functions can contribute to inflammatory conditions and

diseases including asthma, inflammation, and other conditions (Lowe and Cheng, *Drugs of the Future*, 17(9), 799-807, 1992). It has been shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators. Increased levels of cAMP also leads to the relaxation of airway smooth muscle.

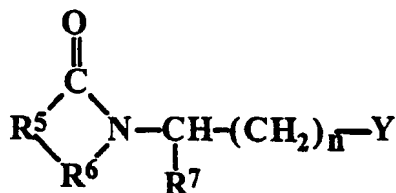
5 The primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases(PDE). There are seven known members of the family of PDEs. It is recognized, for example, that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle. Thus, compounds that inhibit PDE IV specifically,
10 would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardio-vascular or anti-platelet effects. Currently used PDE IV inhibitors lack the selective action at acceptable therapeutic doses.

The compounds of the present invention are useful in the inhibition of phosphodiesterases, particularly PDE III and PDE IV, and in the treatment of disease states mediated thereby.

15 Detailed Description

The present invention is based on the discovery that a class of non-polypeptide imides more fully described herein appear to inhibit the action of $\text{TNF}\alpha$.

The present invention pertains to compounds of the formula:



20 in which:

Y is $\text{---C}\equiv\text{N}$ or $\text{---C(=O)(CH}_2)_m\text{CH}_3$;

m is 0-3;

25 R^5 is: (i) *o*-phenylene, unsubstituted or substituted with one or more substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl

of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; (ii) the divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms; (iii) a divalent cycloalkyl of 4 - 10 carbon atoms, unsubstituted or substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, phenyl or halo; (iv) di-substituted vinylene, substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; or (v) ethylene, unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino, substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo;

R^6 is $-CO-$, $-CH_2-$, $-CH_2CO-$, or $-SO_2-$;

R^7 is (i) straight or branched alkyl of 1 to 12 carbon atoms; (ii) cyclic or bicyclic alkyl of 4 to 12 carbon atoms; (iii) pyridyl; (iv) phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, straight, branched, cyclic, or bicyclic alkyl of 1 to 10 carbon atoms, straight, branched, cyclic, or bicyclic alkoxy of 1 to 10 carbon atoms, CH_2R where R is a cyclic or bicyclic alkyl of 1 to 10 carbon atoms, or halo; (v) benzyl substituted with one to three substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo; (vi) naphthyl; or (vii) benzyloxy;

and,

where n has a value of 0, 1, 2, or 3;

A first preferred subclass pertains to compounds in which:

Y is $-C\equiv N$;

R^5 is o-phenylene, substituted or unsubstituted;

R^6 is $-CO-$ or $-CH_2-$;

R' is an aryl; and

n is 1.

Typical compounds of this invention include:

	R ⁶	R ⁷
5	-CO-	3,4-dimethoxyphenyl
	-CO-	3-ethoxy-4-methoxyphenyl
	-CH ₂ CO-	3,4-dimethoxyphenyl
	-CH ₂ CO-	3-ethoxy-4-methoxyphenyl
	-CO-	3-propoxy-4-methoxyphenyl
10	-CH ₂ CO-	3-propoxy-4-methoxyphenyl
	-CO-	3-cyclopentoxo-4-methoxyphenyl (cyclopentoxo = cyclic C ₅ H ₉ O-)
	-CH ₂ CO-	3-cyclopentoxo-4-methoxyphenyl
	-CO-	3,4-dimethylphenyl
	-CO-	3-ethoxy-4-cyanophenyl
15	-CH ₂ -	3,4-dimethoxyphenyl
	-CH ₂ -	3-ethoxy-4-methoxyphenyl
	-CH ₂ -	3,4-dimethylphenyl

The term alkyl as used herein denotes a univalent saturated branched or straight hydrocarbon chain. Unless otherwise stated, such chains can contain from 1 to 18 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, and the like. When qualified by "lower", the alkyl group will contain from 1 to 6 carbon atoms. The same carbon content applies to the parent term "alkane" and to derivative terms such as "alkoxy".

The term cycloalkyl (or cyclic alkyl) as used herein denotes a univalent saturated cyclic hydrocarbon chain. Unless otherwise stated, such chains can contain from 1 to 18 carbon atoms. Representative of such cycloalkyl groups are methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, cyclotridecyl, cyclotetradecyl, cyclopentadecyl, cyclohexadecyl, cycloheptadecyl, cyclooctadecyl, cyclic terpenes, and the like. When qualified by "lower", the cycloalkyl group will contain from 3 to 6 carbon atoms. The same carbon content applies to the parent term "cycloalkane" and to derivative terms such as "cycloalkoxy".

The compounds can be used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNF α and/or phosphodiesterase. The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including

antibiotics, steroids, etc., to a mammal in need of treatment. Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms. Isotonic saline solutions containing 20-100 milligrams/milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 1 to about 1000 milligrams/day as needed in single or multiple daily administration. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF α activity for other TNF α mediated disease states by the compounds of the present invention. Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia such as levels of reverse transcriptase or viral proteins, and/or for progression of cytokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is observed following the normal treatment regimen, then the amount of cytokine activity interfering agent administered is increased, *e.g.*, by fifty percent a week.

The compounds of the present invention can also be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNF α production, such as viral infections, for example those caused by the herpes viruses or viral conjunctivitis, psoriasis, other skin disorders and diseases, *etc.*

The compounds can also be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of TNF α production. TNF α mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

Certain of these compounds possess centers of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereoisomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbent. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral

acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, alpha-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as to obtain either or both isomers substantially free of the other; *i.e.*, in a form having an optical purity of >95%.

Prevention or inhibition of production of $\text{TNF}\alpha$ by these compounds can be conveniently assayed using methods known in the art. For example, $\text{TNF}\alpha$ Inhibition Assays in LPS stimulated PBMC have been performed as follows:

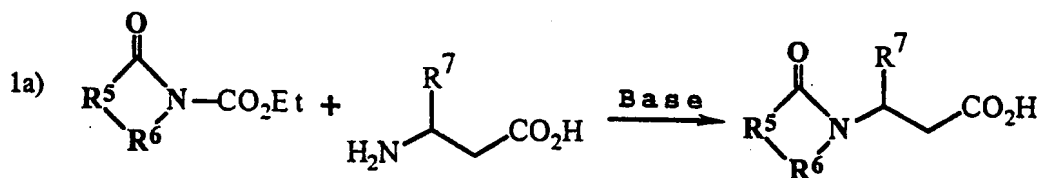
PBMC isolation: PBMC from normal donors were obtained by Ficoll-Hypaque density centrifugation. Cells were cultured in RPMI supplemented with 10% AB+ serum, 2mM L-glutamine, 100 U/mL penicillin and 100 $\mu\text{g/mL}$ streptomycin.

PBMC suspensions: Drugs were dissolved in DMSO (Sigma Chemical), further dilutions were done in supplemented RPMI. The final DMSO concentration in the presence or absence of drug in the PBMC suspensions was 0.25 wt %. Drugs were assayed at half-log dilutions starting at 50 $\mu\text{g/mL}$. Drugs were added to PBMC (10^6 cells/mL) in 96 wells plates one hour before the addition of LPS.

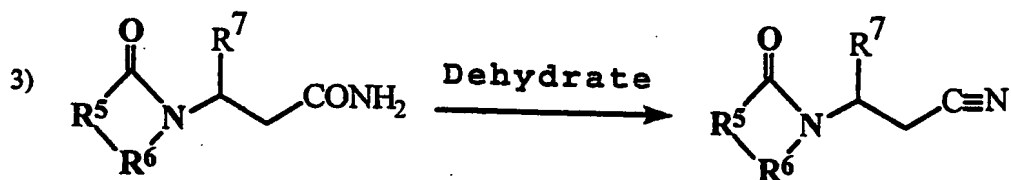
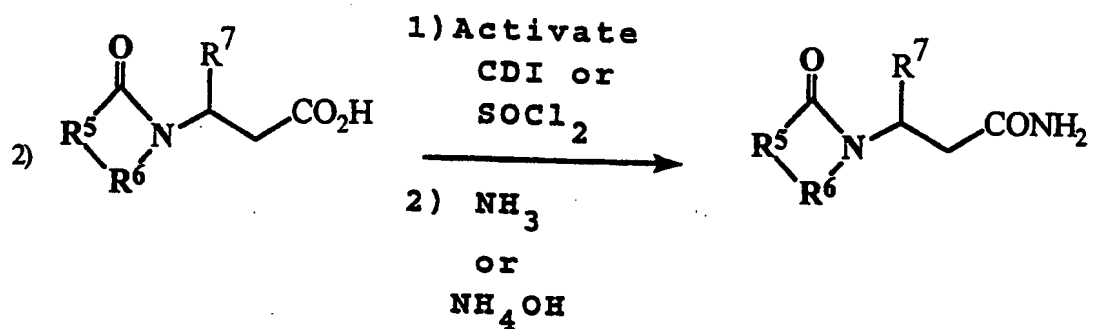
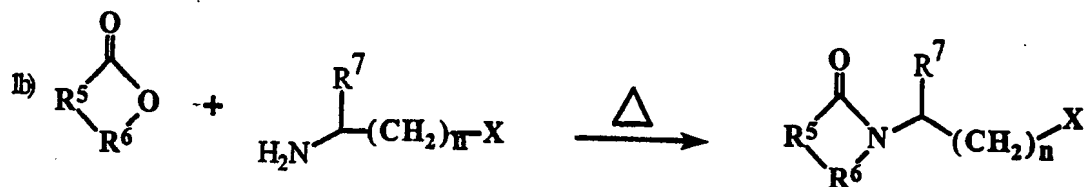
Cell stimulation: PBMC (10^6 cells/mL) in the presence or absence of drug were stimulated by treatment with 1 $\mu\text{g/mL}$ of LPS from *Salmonella minnesota* R595 (List Biological Labs, Campbell, CA). Cells were then incubated at 37°C for 18-20 hours. Supernatants were then harvested and assayed immediately for $\text{TNF}\alpha$ levels or kept frozen at -70°C (for not more than 4 days) until assayed.

$\text{TNF}\alpha$ Determination: The concentration of $\text{TNF}\alpha$ in the supernatant was determined by human $\text{TNF}\alpha$ ELISA kits (ENDOGEN, Boston, MA) according to the manufacturer's directions.

The compounds can be prepared using methods which are known in general for the preparation of nitriles. General reaction schemes are illustrated by the formulas:



or



5 where X is CO₂H, CONH₂, or CN

The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

Example 1**3-Phthalimido-3-(3,4-diethoxyphenyl)propionitrile.**

To an ice bath cooled stirred suspension of 3-phthalimido-3-(3,4-diethoxyphenyl)propionamide (0.96 g, 2.5 mmol) and 4-methylmorpholine (0.66 mL, 6 mmol) in DMF (9 mL) under nitrogen, was added thionyl chloride (0.35 mL, 4.8 mmol) dropwise. There was a slight exotherm after which the mixture was stirred at 0 - 5°C for 30 minutes and at room temperature for 2 hours. The reaction was monitored by HPLC (Waters Nova-Pak/C-18 column, 3.9x150 mm, 4 micron, 1 mL/min, 240 nm, 50/50 CH₃CN/H₃PO₄ 0.1%(aq)). The reaction mixture was poured into a mixture of NaHCO₃ (8.5 mL) and ice (40 g) and stirred until the ice had melted. The mixture was filtered and the solid was washed with copious amounts of H₂O. The wet solid was dissolved in CH₂Cl₂ (25 mL) and the organic layer was separated and dried over MgSO₄ and concentrated *in vacuo* to a sticky semi-solid. The solid was purified twice by flash column chromatography (silica gel, 3% ethyl acetate/methylene chloride) to afford a solid which was dried *in vacuo* (50°C, < 1 mm) to afford 0.5 g (55%) of product as a pale yellow solid; ¹H NMR (CDCl₃) δ 7.91-7.65(m, 4H), 7.12-6.98(m, 2H), 6.90-6.78(m, 1H), 5.61(dd, J = 6.4, 10.3 Hz, 1H), 4.19-3.96(m, 4H), 3.83(dd, J = 10.3, 16.8 Hz, 1H), 3.26(dd, J = 6.4, 16.8 Hz, 1H), 1.55-1.30(m, 6H); ¹³C NMR (CDCl₃) δ 167.7, 149.2, 148.9, 134.3, 131.5, 129.1, 123.6, 120.2, 116.9, 113.2, 112.9, 64.7, 64.5, 51.1, 21.1, 14.7; HPLC 98.4 %. Anal. Calcd for C₂₁H₂₀N₂O₄. Theoretical : C, 69.22; H, 5.53; N, 7.69. Found : C, 69.06; H, 5.48; N, 7.58.

20

Example 2**3-Phthalimido-3-(3,4-dimethoxyphenyl)propionitrile**

To an ice bath cooled stirred suspension of 3-phthalimido-3-(3,4-dimethoxyphenyl)propionamide (1.77 g, 5.00 mmol) and 4-methylmorpholine (1.3 mL, 12 mmol) in DMF (17 mL) under N₂, was added thionyl chloride (0.7 mL, 9.6 mmol) dropwise via a syringe. There was a slight exotherm and after 30 minutes the cooling bath was removed and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into a mixture of NaHCO₃ (17 g) and 75 mL of ice water and stirred until the ice had melted. The

slurry was filtered and the solid was washed with copious amounts of H₂O. The wet solid was dissolved in CH₂Cl₂ (50 mL) and the organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo* to afford an orange solid. The solid was purified by flash column chromatography (silica gel, 5/95 EtOAc/CH₂Cl₂, 50 mm id column) to afford 1.32 g (79%) of the product as a white solid: ¹H NMR (CDCl₃) δ 7.9-7.6(m, 4H), 7.10 (m, 2H), 6.83 (m, 1H), 5.64 (dd, J = 6.5, 10.2 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.82 (dd, 1H), 3.30 (dd, J = 6.5, 16.8 Hz, 1 H); ¹³C NMR (CDCl₃) δ 167.7, 149.5, 149.2, 134.4, 131.5, 129.1, 123.6, 120.1, 116.9, 111.1, 110.7, 56.0, 55.9, 51.1, 21.1. Anal. Calcd for C₁₉H₁₆N₂O₄·0.18 H₂O. Theoretical: C, 76.2; H, 4.85; N, 8.25. Found : C, 67.23; H, 4.79; N, 8.27.

10

Example 3

3-(3'-Nitrophthalimido)-3-(3'-ethoxy-4'-methoxyphenyl)propionitrile

A stirred suspension of 3-nitrophthalic anhydride (0.24 g, 1.13 mmol) and 3-amino-3-(3'-ethoxy-4'-methoxyphenyl)propionitrile (0.25 g, 1.13 mmol) in 6 mL of acetic acid was heated to reflux under nitrogen for 12 hours. The acetic acid was removed *in vacuo* to afford an orange gum which was dissolved in methylene chloride (10 mL) and was washed with a saturated aqueous solution of sodium bicarbonate (2 x 10 mL). The organic layer was separated and the aqueous layer was extracted with methylene chloride (10 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford a yellow oil. The crude product was purified by flash column chromatography (silica gel, 5% ethyl acetate/methylene chloride) and the resulting solid was dried *in vacuo* (60°C, < 1 mm) to afford 0.25 g (56%) of the product as a yellow solid: mp 155.5-157 °C; ¹H NMR (CDCl₃) δ 8.20-8.09 (m, 2 H), 8.02-7.86 (m, 1 H), 7.15-7.02 (m, 2 H), 6.88-6.76 (m, 1 H), 5.64 (dd, J = 6.3, 10.6 Hz, 1 H), 4.09 (q, J = 7 Hz, 2 H), 3.85 (s, 3 H), 3.84 (dd, J = 10.6, 16.7 Hz, 1 H), 3.26 (dd, J = 6.3, 16.7 Hz, 1 H), 1.46 (t, J = 7 Hz, 3 H); ¹³C NMR (CDCl₃) δ 165.3, 162.3, 150.1, 148.7, 144.9, 135.7, 133.5, 129.0, 128.1, 127.4, 123.2, 120.3, 116.6, 112.1, 111.5, 64.6, 55.9, 51.9, 20.9, 14.7; Anal. calcd for C₂₀H₁₇N₃O₆. Theoretical: C, 60.76; H, 4.33; N, 10.63. Found: C, 60.59; H, 4.22; N, 10.65.

Example 4**3-(3'-Aminophthalimido)-3-(3'-ethoxy-4'-methoxyphenyl)propionitrile**

To a solution of 3-(3'-nitrophthalimido)-3-(3'-ethoxy-4'-methoxyphenyl)propionitrile (0.2 g, 0.5 mmol) in 30 mL of ethyl acetate was added 0.05 g of 10% palladium on carbon catalyst. The mixture was hydrogenated in a Parr-Shaker apparatus at 55-60 psi of hydrogen overnight. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to afford a yellow oil. The crude product was purified by flash column chromatography (silica gel, 3% ethyl acetate/methylene chloride). The resulting yellow solid was then dried *in vacuo* (60°C, < 1 mm) to afford 0.09 g (50%) of the product: mp 171-172.5 °C; ¹H NMR (CDCl₃) δ 7.47-7.35 (m, 1 H); 7.19-7.00 (m, 3 H), 6.90-6.29 (m, 2 H), 5.56 (dd, J = 6.6, 10 Hz, 1 H), 5.24 (s, 2H), 4.09 (q, J = 7 Hz, 2 H), 3.84 (s, 3 H), 3.77 (dd, J = 10, 16.8 Hz, 1 H), 3.27 (dd, J = 6.6, 16.8 Hz, 1 H), 1.45 (t, J = 7 Hz, 3 H); ¹³C NMR (CDCl₃) δ 169.4, 167.9, 149.6, 148.5, 145.5, 135.5, 132.1, 129.4, 121.3, 120.0, 117.1, 113.0, 112.2, 111.4, 110.6, 64.5, 55.9, 50.7, 21.1, 14.7; HPLC (Waters Nova-Pak C₁₈ column, 3.9 x 150 mm, 4 micron, 1 mL/min, 240 nm, 40/60, CH₃CN/0.1% H₃PO_{4(aq)}) 4.5 min, 100%; Anal. calcd. for C₂₀H₁₉N₃O₄. Theoretical: C, 65.74, H, 5.24, N, 11.50. Found: C, 65.54; H, 5.23; N, 11.23.

Example 5**3-Phthalimido-3-(3'-ethoxy-4'-methoxyphenyl)propionitrile**

Oxalyl chloride (0.49 mL, 5.64 mmol) was added dropwise to an ice bath cooled stirred solution of DMF (0.48 mL, 6.16 mmol) in acetonitrile (10 mL). A white precipitate formed immediately and was accompanied by gas evolution. The mixture was stirred for 30 minutes at 2-3 °C and then a solution of 3-phthalimido-3-(3'-ethoxy-4'-methoxyphenyl)propionamide (1.89 g, 5.13 mmol) in DMF (15 mL) was added slowly. After 10 minutes pyridine was added and the mixture was stirred for 30 minutes at 2-3 °C. The reaction mixture was then poured into 60 mL of ice and stirred for 20 minutes. The slurry was filtered and the solid was washed with water, air dried and then dried *in vacuo* (60 °C, < 1mmHg) to afford 1.7 g (95%) of the product as a white solid: mp 135-137 °C; ¹H NMR (CDCl₃) δ 7.86-7.71 (m, 4 H), 7.08-7.05 (m, 2 H), 6.84-6.81 (m, 1 H), 5.63 (dd, J = 6.5, 10.3 Hz, 1 H), 4.11 (q, J = 7 Hz, 2 H), 3.88-3.77 (m, 1 H), 3.84 (s, 3 H), 3.32-

3.23 (m, 1 H), 1.45 (t, J = 7 Hz, 3 H); ^{13}C NMR (DMSO- d_6) δ 167.4, 149.0, 147.8, 134.9, 130.8, 129.2, 123.5, 119.4, 118.2, 112.1, 111.7, 63.8, 55.4, 50.0, 20.5, 14.6; Anal. calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$. Theoretical: C, 68.56, H, 5.18, N, 8.00. Found: C, 68.46; H, 5.37; N, 8.02.

Example 6

5 1-(1'-Oxo-isoindoline)-1-(3', 4'-dimethoxyphenyl)propionitrile

To an ice cooled stirred suspension of 1-(1'-oxo-isoindoline)-1-(3', 4'-dimethoxyphenyl)propionamide (1.7 g, 5.0 mmol) and 4-methylmorpholine (1.3 mL, 12 mmol) in DMF (20 mL) under N_2 , was added thionyl chloride (0.7 mL, 9.6 mmol) dropwise via a syringe. There was a slight exotherm and after 1 hour the cooling bath was removed and the reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was poured into 100 mL of ice and stirred until the ice had melted. The slurry was filtered and the solid was washed with copious amounts of water. The solid was purified twice by flash column chromatography (silica gel, 1/9 and 24/76, EtOAc/ CH_2Cl_2). The resulting solid was dried *in vacuo* to afford 0.97 g (60%) of the product as an orange tan solid: mp 119-121 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 7.94-7.85 (m, 1 H), 7.61-7.30 (m, 3H), 7.05-6.85 (m, 3 H), 5.73 (t, J = 7 Hz, 1 H), 4.46 (d, J = 16.7 Hz, 1H), 4.19 (d, J = 16.7 Hz, 1 H), 3.89 (s, 3H), 3.86 (s, 3H), 3.23(m, 2 H); ^{13}C NMR (CDCl_3) δ 168.5, 149.5, 149.4, 141.1, 131.9, 131.8, 128.7, 128.2, 123.9, 122.9, 119.1, 117.4, 111.2, 111.0, 56.0, 55.9, 51.6, 47.3, 21.1; Anal. calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$. Theoretical: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.26; H, 5.56; N, 8.47.

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Example 7

1-(1'-Oxo-isoindoline)-1-(3'-ethoxy-4'-methoxyphenyl)propionitrile

To an ice cooled stirred suspension of 1-(1'-oxo-isoindoline)-1-(3'-ethoxy-4'-methoxyphenyl)propionamide (1.0 g, 2.8 mmol) and 4-methylmorpholine (0.75 mL, 6.8 mmol) in DMF (10 mL) under N_2 , was added thionyl chloride (0.4 mL, 5.5 mmol) dropwise via a syringe. There was a slight exotherm and after 1 hour the cooling bath was removed and the reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was poured

into 100 mL of ice and stirred until the ice had melted. The slurry was filtered and the solid was washed with copious amounts of water. The solid was purified by flash column chromatography (silica gel, 1.5/8.5, EtOAc/CH₂Cl₂). The resulting solid was dried *in vacuo* to afford 0.57 g (60%) of the product as an ivory solid: mp 125-125.5°C; ¹H NMR (CDCl₃) δ 7.88 (d, J = 7 Hz, 1 H), 7.60-7.30 (m, 3H), 7.05-6.80 (m, 3 H), 5.71 (t, J = 6.9 Hz, 1 H), 4.45 (d, J = 14 Hz, 1H), 4.20-4.00 (m, 3 H), 3.87 (s, 3H), 3.23 (m, 2 H), 1.44 (t, 7 Hz, 3 H); ¹³C NMR (CDCl₃) δ 168.5, 149.7, 148.8, 141.2, 131.9, 131.8, 128.6, 128.2, 123.9, 122.9, 119.2, 117.4, 112.4, 111.5, 64.6, 55.9, 51.6, 47.3, 21.1, 14.6; Anal. calcd for C₂₀H₂₀N₂O₃. Theoretical: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.11; H, 5.91; N, 8.17.

Example 8

Tablets, each containing 50 milligrams of active ingredient, can be prepared in the following manner:

Constituents (for 1000 tablets)

active ingredient	50.0 grams
lactose	50.7 grams
wheat starch	7.5 grams
polyethylene glycol 6000	5.0 grams
talc	5.0 grams
magnesium stearate	1.8 grams
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, the lactose, the talc, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 milliliters of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 9

Tablets, each containing 100 milligrams of active ingredient, can be prepared in the following manner:

5	<u>Constituents</u> (for 1000 tablets)	
	active ingredient	100.0 grams
	lactose	100.0 grams
	wheat starch	47.0 grams
	magnesium stearate	3.0 grams

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, the lactose, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 milliliters of water and this suspension is added to 100 milliliters of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 10

Tablets for chewing, each containing 75 milligrams of active ingredient, can be prepared in the following manner:

20	<u>Composition</u> (for 1000 tablets)	
	active ingredient	75.0 grams
	mannitol	230.0 grams
	lactose	150.0 grams
	talc	21.0 grams
	glycine	12.5 grams
25	stearic acid	10.0 grams
	saccharin	1.5 grams
	5% gelatin solution	q.s.

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50°C and again forced through a sieve of 1.7 mm mesh width. The active ingredient, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is

mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

Example 11

5 Tablets, each containing 10 milligrams of active ingredient, can be prepared in the following manner:

Composition (for 1000 tablets)

	active ingredient	10.0 grams
	lactose	328.5 grams
	corn starch	17.5 grams
10	polyethylene glycol 6000	5.0 grams
	talc	25.0 grams
	magnesium stearate	4.0 grams
	demineralized water	q.s.

15 The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced
20 through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 12

Gelatin dry-filled capsules, each containing 100 milligrams of active ingredient, can be prepared in the following manner:

25	<u>Composition</u> (for 1000 capsules)	
	active ingredient	100.0 grams
	microcrystalline cellulose	30.0 grams
	sodium lauryl sulphate	2.0 grams
	magnesium stearate	8.0 grams

The sodium lauryl sulphate is sieved into the active ingredient through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 milligrams each into size 0 (elongated) gelatin dry-fill capsules.

Example 13

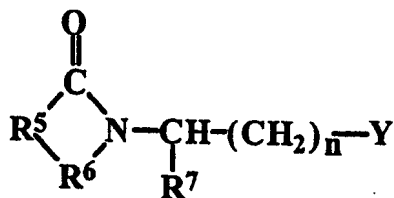
A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

10	active ingredient	5.0 grams
	sodium chloride	22.5 grams
	phosphate buffer pH 7.4	300.0 grams
	demineralized water	to 2500.0 milliliters

15 The active ingredient is dissolved in 1000 milliliters of water and filtered through a microfilter or slurried in 1000 mL of H₂O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare dosage unit forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 milligrams of active ingredient).

What is claimed is:

Claim 1. A composition having the formula:



wherein:

Y is $-\text{C}\equiv\text{N}$ or $-\overset{\text{O}}{\parallel}{\text{C}}(\text{CH}_2)_m\text{CH}_3$;
 m is 0-3;

R⁵ is: (i) *o*-phenylene, unsubstituted or substituted with one or more substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxy, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; (ii) the divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms; (iii) a divalent cycloalkyl of 4 - 10 carbon atoms, unsubstituted or substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, phenyl or halo; (iv) di-substituted vinylene, substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxy, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; or (v) ethylene, unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxy, carboxy, hydroxy, amino, amino, substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo;

R⁶ is $-\text{CO}-$, $-\text{CH}_2-$, $-\text{CH}_2\text{CO}-$, or $-\text{SO}_2-$;

R⁷ is (i) straight or branched alkyl of 1 to 12 carbon atoms; (ii) cyclic or bicyclic alkyl of 4 to 12 carbon atoms; (iii) pyridyl; (iv) phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, straight, branched, cyclic, or bicyclic alkyl of 1 to 10 carbon atoms, straight, branched, cyclic, or bicyclic alkoxy of 1 to 10 carbon atoms, CH_2R where R is a cyclic or bicyclic alkyl of 1 to 10 carbon atoms, or halo; (v) benzyl substituted with one to three substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo; (vi) naphthyl; or (vii) benzylloxy;

38 and,
39 where n has a value of 0, 1, 2, or 3;

1 Claim 2. The method of reducing levels of $\text{TNF}\alpha$ in a mammal which comprises
2 administering thereto an effective amount of a compound of Claim 1.

1 Claim 3. A pharmaceutical composition comprising an amount of a compound according
2 to claim 1 effective upon single or multiple dosage to inhibit $\text{TNF}\alpha$.

1 Claim 4. The method of inhibiting phosphodiesterase in a mammal which comprises
2 administering thereto an effective amount of a compound of Claim 1.

1 Claim 5. A pharmaceutical composition comprising an amount of a compound according
2 to claim 1 effective upon single or multiple dosage to inhibit phosphodiesterase.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/14077

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/48 A61K31/40 C07D209/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 110 219 A (BASF AG) 13 June 1984 * claims (A = branched alkyl) *	1
A	WO 95 01348 A (CELGENE CORPORATION) 12 January 1995 see claim 26	1,3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 December 1996

Date of mailing of the international search report

18.12.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/14077

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 2 and 4 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/14077

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-110219	13-06-84	DE-A- 3242477 CA-A- 1207326 JP-A- 59108765 US-A- 4563474	24-05-84 08-07-86 23-06-84 07-01-86

WO-A-9501348	12-01-95	AU-A- 7216794 CA-A- 2166315 EP-A- 0706521 FI-A- 956362 PL-A- 312386 US-A- 5463063	24-01-95 12-01-95 17-04-96 26-02-96 15-04-96 31-10-95
